PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	Docket No: Q65721
Praveen SHARMA, *et al.*	
U.S. Patent Appln. No.: 10/727,576	Group Art Unit: 1634
Confirmation No.: 8084	Examiner: Juliet Caroline SWITZER
Filed: December 5, 2003	

For: METHOD OF PREPARING A STANDARD DIAGNOSTIC GENE TRANSCRIPT PATTERN

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 41.37, Appellant submits the following:

Table of Contents

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, DIAGENIC AS (having a business address of Ostensjoveien 15B, 0661 Oslo, NORWAY), by virtue of an Assignment recorded on April 9, 2002, at Reel: 012777, Frame: 0909.

II. RELATED APPEALS AND INTERFERENCES

To the knowledge and belief of Appellant, the Assignee, and the Appellant's legal representative, there are no other appeals or interferences before the Board of Appeals and Interferences that will directly affect or be affected by the Board's decision in the instant Appeal.

III. STATUS OF CLAIMS

Claims 1-17 and 36-38 have been canceled.

Claims 18-35 are pending and are rejected in the application.

This is an Appeal from the Examiner's rejections of claims 18-35 under 35 U.S.C. § 103(a).

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final Office Action of January 12, 2010.

The Appendix included with this Brief sets forth the claims involved in the appeal and reflects all of the claim amendments that have been entered by the Examiner.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention relates to non-invasive methods of obtaining isolated probes from transcripts that are differentially expressed in very early stage breast cancer versus a normal patient (i.e., patient to be diagnosed), and preparing a gene transcript pattern kit that comprises preparing a solid support that carries the isolated probes. See paragraph bridging pages 2-3 to page 5, 1st full paragraph, page 5, last full paragraph, page 7, 1st full paragraph, page 8, 1st full paragraph, pages 15, paragraph bridging page 19 to page 23 and Example 5 at pages 35-37 of the specification. The gene transcript pattern kits are used to prepare gene transcript patterns for the diagnosis or identification of breast cancer from the very early stage of the disease. Id.

The advantage of the non-invasive methods of the present invention is that samples of distant tissue or body fluids of an individual that are not affected by a disease condition, e.g., a tumor, may be obtained and diagnostic standard probes designed in order to diagnose or identify breast cancer at a very early stage of the disease. See page 10, last three paragraphs and page 11, 3rd full paragraph, page 15, lines 11-14, page 23, 2nd full paragraph of the specification. Specifically, the claimed methods allow for the detection of very early stage breast cancer when the disease is non-metastatic or pre-metastatic.

Independent claim 18 relates to a method of obtaining isolated selected mRNA species or isolated cDNA species useful for diagnosing or identifying breast cancer in a human. Differentially expressed transcripts in a human known to have very early stage breast cancer versus a normal human to be diagnosed, are identified using blood samples that are obtained distant to the area of disease, e.g., tumor. See paragraph bridging pages 2-3, paragraph bridging pages 3-4, page 5, 1st full paragraph, page 7, 1st full paragraph, pages 12-13, Example 5 at pages 35-36 of the specification. Informative probes are selected from the transcripts which exhibit altered expression at the very early stage of breast cancer, and there is no requirement to select

the probes in a particular way, as the invention does not lie in the particular probes that are isolated, but rather in the use of blood samples that are distantly located from the area of the disease. See page 5, 1st full paragraph, page 7, 1st full paragraph, page 10, 3rd-5th full paragraphs, page 11, 3rd full paragraph, page 15 to page 16, 2nd full paragraph of the specification.

Independent claim 19 relates to a method of preparing a gene transcript pattern probe kit comprising preparing at least one solid support carrying the isolated selected mRNA species or isolated selected cDNA species to form a gene transcript pattern probe kit. See paragraph bridging pages 2-3, page 11, last paragraph, paragraph bridging page 16 to page 19, 2nd full paragraph, Example 5 at pages 36-37 of the specification. The gene transcript pattern kit is then used to diagnose breast cancer by preparing a gene transcript pattern or fingerprint. Specifically, a standard gene transcript pattern or standard diagnostic probe pattern (SDPP) characteristic of very early stage breast cancer is prepared, and compared to a test gene transcript pattern or patient specific probe pattern (PSPP) that is prepared from a normal patient to be diagnosed in order to determine a degree of correlation that is indicative of very early stage breast cancer. See paragraph bridging pages 2-3, page 3, 2nd full paragraph and page 4, 1st full paragraph to page 5, 3rd full paragraph, paragraph bridging page 19 to page 23, Figure 1, Example 5 at page 37 of the specification.

Although the above summary refers to portions of the specification, these references should not be considered to be limiting. Rather, they reflect examples of the disclosed embodiments.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. An issue on appeal is whether the Office improperly finally rejected claims 18 and 20-25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,190,857 to Ralph *et al.* (hereinafter "Ralph") in view of Lukas *et al.* (*Journal of Investigative Medicine*, 45(1): 132A (1997); hereinafter "Lukas").

2. An issue on appeal is whether the Office improperly finally rejected claims 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ralph in view of Lukas as applied to claims 18 and 20-25, and further in view of Wadhwa *et al.* (*Molecular Biotechnology*, 6: 213-217 (1996); hereinafter "Wadhwa").

VII. ARGUMENT

A. The rejection of claims 18 and 20-25 under 35 U.S.C. §103(a) as allegedly being unpatentable over Ralph and Lukas should be reversed because a *prima facie* case of obviousness has not been established.

Independent claim 18 recites, in part, a method of obtaining isolated selected mRNA species or isolated selected cDNA species useful for diagnosing or identifying breast cancer in a human comprising the steps of isolating mRNA from cells from blood of more than one human who are known to have very early stage breast cancer (breast cancer sample); isolating mRNA from corresponding cells from blood of more than one normal human (normal sample); selecting 10 or more mRNA species or 10 or more cDNA species from the resulting separated mRNA species or resulting separated cDNA species, which are present at a different level in the normal sample than in the breast cancer sample by identifying a signal corresponding to each mRNA species or cDNA species; and isolating the resulting 10 or more selected mRNA species or resulting 10 or more selected cDNA species to obtain isolated selected mRNA species or isolated selected cDNA species.

Independent claim 19 recites the same steps and further comprises a step of preparing at least one solid support carrying the resulting isolated selected mRNA species or isolated selected cDNA species to form a gene transcript pattern probe kit.

The Examiner contends that the arguments and Declarations of Dr. Mackay of record are not commensurate in scope with "most" of the claims which are directed to methods of screening the blood to identify differentially expressed transcripts that are markers for breast cancer, and not towards diagnosis of early stage breast cancer. See At pages 3 and 5 of the Office Action mailed January 12, 2010. To the contrary, Applicants note that the arguments and evidence of record are commensurate in scope to the claimed invention because the present application

provides a method of identifying transcripts or probes from a breast cancer sample that serve as a set of markers for diagnosis of very early stage breast cancer, as well as a method of preparing a gene transcript pattern kit to provide a transcript pattern standard for diagnosis of very early stage breast cancer using the transcripts or probes identified. See pages 3-4 and Examples of the original specification. The differentially expressed transcripts or probes identified are bound to a solid support and then hybridized to mRNA so that the amount of nucleic acid material that binds to the transcripts or probes is assessed and forms a transcript pattern standard of that disease or condition to be used for diagnosis. See pages 3-4 and Examples of the specification; and Declaration of Dr. Sharma filed September 21, 2007.

For at least the reasons below, the Examiner has failed to establish a *prima facie* case of obviousness. Also, even if, *arguendo*, a *prima facie* case is established, the unexpected detection of non-metastatic or pre-metastatic, very early stage breast cancer achieved by the claimed methods is evidence of the non-obviousness of the present invention.

A *prima facie* showing of obviousness requires (1) a teaching or suggestion of all claimed limitations; (2) a suggestion or motivation in the references or in the knowledge of one of ordinary skill in the art, to modify the references or to combine reference teachings; and (3) a reasonable expectation of success.

1. Ralph and Lukas do not teach or suggest all the claim limitations.

The Examiner has ***admitted that Ralph does not teach***: (1) a method in which the organ defined cancer is very early stage breast cancer, (2) a method in which at least ten differently expressed markers are isolated, or (3) a method in which between 50 and 100 or between 10 and 500 mRNA or cDNA species are selected. See page 6, lines 9-12 of Office Action mailed

February 8, 2008. Also, the Examiner ***has admitted that "there is not [sic] exemplification of the method for very early stage breast or relevant diseases which includes breast cancer [in Ralph]."*** See sentence bridging pages 3-4 of Office Action mailed January 12, 2010. In ascertaining the differences between the claimed invention and the art, the Examiner has failed to interpret the claim language as required, and consider both the invention and the art as a whole. See MPEP §§ 2111 and 2141.02. In the present case, by the Examiner's own admissions, the teachings of Ralph as a whole do not teach or suggest the limitations of the claimed invention.

Lukas is merely cited by the Examiner to establish that there was a desire at the time the invention was made to identify molecular markers for very early stage breast cancer. See page 4, lines 1-3 of Office Action mailed January 12, 2010. However, even though Lukas teaches markers or differentially expressed genes involved in very early stage breast cancer, Lukas is entirely silent as to whether blood cells in a patient with breast cancer would have modified expression, or that such modified expression has diagnostic value. See footnote at page 5 of Response filed December 1, 2009. Specifically, Lukas is silent regarding isolating mRNA from blood cells of more than one human who are known to have very early stage breast cancer (breast cancer sample), and isolating mRNA from corresponding blood cells of more than one normal human (normal sample), as claimed.

In view of the deficiencies recognized above for Ralph and Lukas, and for at least the reasons discussed in further detail below, neither Ralph nor Lukas, separately or in combination, teach or suggest all the limitations of the claimed method of obtaining isolated probes from a blood sample that serve as a set of markers for diagnosis of very early stage breast cancer.

2. Because Ralph does not teach or suggest detection of non-metastatic or pre-metastatic very early stage breast cancer, and makes clear that the early stage of disease would encompass a metastasizing tumor, there would have been no reasonable expectation of success of detecting very early stage breast cancer.

First, as discussed in detail below, one of ordinary skill in the art would only have extrapolated the teachings of Ralph to other cancers that are at a similar stage, i.e., cancers which have reached a metastatic phenotype and hence have detectable markers of that metastatic phenotype. This does not include very early stage breast cancer (see paragraphs 11 and 16 of Second Declaration by Dr. Mackay filed December 1, 2009). Early stage disease as referred to by Ralph would be interpreted in the context of cancer that has metastasized (see paragraph 12 of Second Declaration of Dr. Mackay filed December 1, 2009). Accordingly, the Examiner's extrapolation of the teachings of Ralph to the detection of cancers which have not reached a metastatic phenotype, e.g., very early stage breast cancer, as claimed, constitutes impermissible hindsight. M.P.E.P. § 2145.

Second, Ralph as a whole does not teach or suggest detection of non-metastatic or pre-metastatic very early stage breast cancer. See First Declaration by Dr. Mackay filed March 27, 2009 and paragraphs 6-15 of Second Declaration by Dr. Mackay filed December 1, 2009. Rather, Ralph only teaches that markers may be detected for metastatic breast and metastatic prostate cancer, i.e., all of the cancers examined by Ralph display a discrete phenotype change to be detectable by the method of Ralph. See paragraph 11, of Second Declaration of Dr. Mackay filed December 1, 2009. As previously noted on the record, there are fundamental differences between metastatic and non-metastatic or pre-metastatic cancers so that metastatic breast cancer cannot be equated to non-metastatic, very early stage breast cancer. When cells become metastatic, their phenotype changes, i.e., cancer cells begin to exhibit intrinsic properties which may be used as clinically detectable indicators of cells which have metastatic potential. See

paragraph 4 of the First Declaration of Dr. Mackay filed March 27, 2009. Specifically, cancers that have reached metastatic potential or are metastatic release cells, debris or cellular components into the blood system allowing for the interaction of blood cells with the cells, debris or cellular components in the peripheral blood system.

In contrast, very early stage breast cancer which is non-metastatic or pre-metastatic does not release such cells, debris or cellular components into the blood system. See paragraphs 7-8 of First Declaration by Dr. Mackay filed March 27, 2009 and paragraph 15 of Second Declaration by Dr. Mackay filed December 1, 2009.

The Examiner erroneously maintains that the claimed invention would have been obvious because Ralph allows for detection and diagnosis of disease states that affect the peripheral blood leukocytes, by detection of markers produced by circulating leukocytes and not diseased cells (column 5, lines 7-11 of Ralph), so that there is no requirement for direct interaction between cancer cells, their debris, or cellular components. See page 3 of Office Action mailed January 12, 2010. According to the Examiner, detection of markers and diagnosis of disease would have been expected at very early stages of disease progression when there are few or no circulating cells present in the peripheral blood. Id. In this regard, the Examiner refutes Applicants' arguments as being contrary to the teachings of Ralph and knowledge in the art, as evidenced by Campbell (Biology, 4th Edition, 1996, page 833) showing it was known in the art that white blood cells would come into contact with tumor cells via the interstitial fluid and the lymphatic system even if no blood vessels invaded the tumor. Id.

As noted on the record, mere contact between a blood cell and a tumor cell is not enough to allow detection by Ralph. Paragraphs 19-21 of the Second Declaration by Dr. Mackay (filed December 1, 2009), points out that pivotal to the success of the method by Ralph is the

requirement for the cancer cell to have reached metastatic potential and thus, to display a metastatic phenotype. It is this metastatic phenotype which is detected or detectable by Ralph. Based on the teachings of Ralph, detailed below, a person of ordinary skill would have expected that it was the debris or cellular components of metastatic cancer cells such as the early prostate cancers examined by Ralph, that are responsible for the effects observed and the method Ralph could only be extended to detecting cancers that have reached metastatic potential or that are metastatic. Thus, even if blood cells did come into contact with very early stage breast cancer cells, no response of the kind observed by Ralph would have been expected, as those cells would not have reached metastatic potential. There is nothing in Ralph that would have guided one of ordinary skill in the art to detect cancers that are phenotypically different and which have not reached metastatic potential. See paragraph 22 of Second Declaration by Dr. Mackay (filed December 1, 2009).

This view is compatible with the teachings of Ralph at column 5, lines 7-11, which the Examiner maintains teaches that detection at very early stages of disease progression may be feasible (see page 3, lines 5-8 of Office Action mailed January 12, 2010). In this passage, Ralph references that it may be possible to use its method at "very early stages of disease progression", but does not say what constitutes such "early stages". In particular there is no clear teaching or suggestion that the method may be applied to very early stage breast cancer. Clearly, from the continuation of the passage in column 5, very early stages encompass diseases in which a few circulating diseased cells are present in the peripheral blood.

Furthermore, the disclosure of Ralph makes clear that very early stage disease would encompass a metastasizing tumor. For example column 52, lines 1-4 states that "[i]n early stages of the disease state, such immune responses may be localized…[f]or example, the response may

be limited to lymph nodes immediately surrounding a metastasizing tumor or other localized form of the disease state". Thus, although the methods of Ralph may be extrapolated to early stage disease, it is not entirely clear what is meant by this and this must be interpreted by the skilled artisan. In this respect, the teachings of Ralph must be interpreted as a whole to determine what is scientifically credible based on its disclosure.

Based on the scientific teachings of Ralph discussed above, a person of ordinary skill would have expected that it was the debris or cellular components of cancer cells (characteristic of early prostate cancers such as those cancers examined by Ralph) which are responsible for the effects observed in Ralph, and Ralph's method could only be extended to detecting cancers which reach metastatic potential or which are metastatic.

This view is not incompatible with the teaching at column 5 of Ralph. In the quoted passage, Ralph refers to two alternatives, namely, (i) when there are few circulating diseased cells and (ii) when there are no circulating diseased cells. The first alternative is entirely in line with Ralph's comments and represents the early stages of metastatic disease. A few circulating metastatic cells are present and these can interact with blood cells. When there are no circulating cells, as in the second alternative, the diseased cells may have still reached metastatic potential and either they or their debris or cellular components may be interacting with leukocytes to cause an immune response in those cells.

Thus, the teachings at colum 5 of Ralph are entirely compatible with extension of Ralph's method to earlier stages of disease than the metastatic stages examined by Ralph, i.e. in which metastatic potential has been reached.

As mentioned above, there is no explicit teaching or suggestion that the method of Ralph could be extended to very early stages of cancer (or specifically very early stage breast cancer) in which neither metastasis nor metastatic potential has been reached.

The column 5 teaching refers to very early stages of disease. However, there is nothing to suggest this should be extrapolated to very early stages of breast cancer. "Very early stage breast cancer" has a very particular meaning, i.e. referring to stage 0 breast cancer (DCIS and LCIS) (this has been acknowledged by the Examiner at paragraph 1 of the Office Action mailed January 12, 2010). If Ralph had intended the reference in column 5 to cover stage 0 breast cancer, then the phrase that follows would not have been used "when there are few or no circulating diseased cells present in the peripheral blood". The blood of stage 0 breast cancer patients would not have a few circulating diseased cells. These cancers are breast cancers in which the cancer cells are entirely confined to ducts of the breast and there are no circulating disease cells.

The Examiner maintains that the same language was used in the present application and Ralph in referring to very early stage disease. Firstly, it should be noted that when Ralph refers to very early stage disease, this is without reference to cancer or breast cancer in particular. There is no reference to very early stage breast cancer anywhere in that document. Furthermore, as mentioned above, the very early stages of disease according to Ralph include stages in which some circulating disease cells are present, unlike the very early stages of breast cancer in which no circulating cells are present. Thus, Ralph uses the reference to very early stage disease in a very different way to the way it is used in the instant claims to reference a particular condition (breast cancer) which denotes a very specific stage, stage 0, of that cancer.

Furthermore, as mentioned above, the teaching at column 52 of Ralph refers to early stages of disease. However, a person of ordinary skill would not interpret this as referring to very early stages of breast cancer in which metastatic potential has not been reached. In column 52, from line 1, Ralph indicates that in early stages of the disease the immune response may be localised. Ralph then refers to a metastasizing tumour. Therefore, Ralph is linking early stages of cancer to those which are metastasizing and not those which have not yet reached metastatic potential as would be the case in very early stage breast cancer stages which are claimed (see paragraphs 7 and 9 of the First Declaration by Dr Mackay filed March 27, 2009).

As noted in the Second Declaration by Dr Mackay filed December 1, 2009 (see paragraph 13), there is no technical teaching from the Examples which have been reported in Ralph that would make a person of ordinary skill think that Ralph intends for its method to be extended to detection of cancers in which metastatic potential has not yet been reached. The comment that it may be feasible to look at very early stages of disease progression where there are few or no circulating cells needs to be viewed in this context, as discussed above. Firstly, it is purely speculative whether very early stages of disease could be detected based on the disclosure of Ralph, and secondly, even if a person of ordinary skill gave this comment credence, it would be considered in view of the whole disclosure of Ralph which could only apply to cancers which have at least reached metastatic potential, e.g. organ defined prostate cancers.

Column 9, line 66 to column 10, line 6 refers to use of the method for analysis of diseases that include, but are not limited to metastatic or organ defined cancer, particularly metastatic prostate cancer. However, in the context of the document, organ defined cancer would be interpreted as prostrate cancer, not breast cancer. Dr Mackay deals with this point in his First Declaration filed March 27, 2009, paragraphs 3 and 4. In brief, Dr Mackay is of the view that

the comments set forth in column 9 referring to organ defined cancer are based on the results obtained with organ confined prostate cancer samples, reported in column 5, from line 61 of Ralph which he assumes relates to the results presented in column 94, line 43 to column 95, line 17 of Ralph. The passage in column 5 of Ralph states that the method allows the identification of patients with organ confined prostate cancer (relative to those with benign prostatic hyperplasia) using analysis of PSA and IL-8 gene products and this is the conclusion of the results presented in columns 94 and 95 of Ralph.

As discussed in paragraph 4 of the First Declaration by Dr. Mackay filed March 27, 2009, the results presented in columns 94 and 95 of Ralph concern patients with stage A to C organ confined prostate cancer. Based on what was known at the time, it would have been understood that a significant proportion of those patients would have already developed metastatic disease. As the patients have already reached metastatic potential or become metastatic, organ confined prostate cancers would fall within the group of cancer that could be detected as such metastatic cancer would have already released cells, their debris or cellular components into the bloodstream, i.e., have cells with metastatic potential or be metastatic in nature, which could interact with leukocytes to provide a detectable alteration in transcript levels.

However as noted at paragraph 7 of the First Declaration by Dr Mackay filed March 27, 2009, disease presentation in prostate and breast cancer is different. Organ confined breast cancer is not equivalent to organ confined prostate cancer. Whereas, in prostate cancer the cells of most organ confined cancers already exhibit metastatic potential or the cancer has already progressed to metastatic disease, in breast cancer, one sees a different spectrum of disease presentation. The vast majority of very small breast cancers detected by regular mammographic screening never develop metastatic disease. The percentage of patients who have involved

lymph nodes at diagnosis is low. Only a few patients with small node negative tumors at diagnosis will go on to develop metastases within 5 years of diagnosis, and these patients are considered to have particularly biologically aggressive disease at diagnosis. However, in the clinical care of breast patients, cancer confined to the organ (that is the breast) covers a very wide spectrum of disease from early to very advanced.

In prostate cancer, many organ confined cancers, even some apparently early stage prostate cancers would have developed to the metastatic stage, i.e. the cells display metastatic potential or the disease is metastatic. In contrast, in breast cancer, few organ confined cancers would have even developed cells with metastatic potential and those that had would be at the advanced stage. Very early stage breast cancer would not present any cells with metastatic potential.

As a consequence on reading the teaching at column 9 of Ralph, a skilled artisan would have understood that the method of Ralph could only be extended to cancers which had reached their metastatic potential. The method is therefore applicable once the first signs of cells with metastatic potential or metastasis appear. Since organ confined breast cancer which is still at an early stage does not have cells with metastatic potential, one would not expect that the peripheral blood cells could come into contact with metastatic breast cancer cells or their debris or cellular components at that stage.

Thus, Ralph makes no reference to the detection of very early stage breast cancers, with good reason. Organ defined breast cancers could not be expected to behave in the same way as organ defined prostate cancers as only the latter would reach metastatic potential in their very early stages. There would therefore be no expectation that the same principle (i.e., evidence of a metastatic phenotype) could be used to identify very early stage breast cancers which did not

have a metastatic phenotype. Extension of the Ralph *et al* teaching to very early stage breast cancer is only possible with hindsight.

Thus, in view of the teachings of Ralph and the examples provided in Ralph, a person of ordinary skill would have understood that the tumor cells would need to be cells with metastatic potential or which were metastatic to be able to be detected by the method of Ralph. Very early stage breast cancer cells are neither. Very early stage breast cancers are pre-metastatic. Clinical evidence supports this. One hundred percent of DCIS may be resolved surgically as DCIS is entirely pre-metastatic. In contrast, only 40-60% of prostate cancers may be cured in this way which is evidence of the metastatic changes which have occurred in those cancers.

The experiments of Ralph only show a correlation between metastatic cancer and markers in the blood indicative of the presence of metastatic cancer. Specifically, Ralph shows comparisons of gene expression levels in blood samples from patients with metastatic prostate or metastatic breast cancer to those in normal blood samples. See also all Examples of Ralph and Ralph at column 5, lines 55-57 (stating "[t]he instant disclosure demonstrates the success of this approach for the detection of metastatic prostate and/or metastatic breast cancer."); column 6, lines 18-20 (stating "[a] number of markers for metastatic cancer of prostate or breast are described in the instant disclosure."); column 6, lines 64 to 65 (stating "provides a simple and effective diagnostic test for the presence of cancer metastases"); column 7, lines 10-12 (stating "[t]he present disclosure represents a substantial and unexpected advance over previous knowledge in this field. It provides a sensitive means for detecting metastatic cancer...differentiating between BPH, localized and advanced forms of prostate cancer").

As discussed above, organ defined breast cancers could not be expected to behave in the same way as organ defined prostate cancers as only the latter would reach metastatic potential in their

very early stages. There would therefore be no expectation that the same principle (*i.e.*, evidence of a metastatic phenotype) could be used to identify very early stage breast cancers which do not have a metastatic phenotype. Thus, Ralph shows that the peripheral blood of patients with metastatic disease exhibit markers which can be used to diagnose that disease.

As discussed above and in the First Declaration by Dr Mackay filed March 27, 2009 (see paragraph 4) and Second Declaration filed December 1, 2009 (see paragraphs 6-15), Ralph is principally concerned with analysis of cancers that have reached metastatic potential or are metastatic-. One of ordinary skill in the art would have appreciated and taken the disclosure in Ralph in context with the rest of the teachings, which is principally concerned with analysis of cancers that have reached metastatic potential or are metastatic, by showing that the peripheral blood of patients with metastatic disease exhibit markers which can be used to diagnose that disease. Specifically, cells that reach metastatic potential can release debris into the peripheral blood system that interact with leukocytes. See First Declaration by Dr. Mackay filed March 27, 2009. Accordingly, because it was known in the art that very early stage breast cancer was not at a metastatic stage, there would have been no reasonable expectation that very early stage breast cancer could be detectable based on a method reliant on detection of metastatic markers, as such markers would be absent in non-metastatic or pre-metastatic very early stage breast cancer. See paragraph 15 of the Second Declaration of Dr. Mackay filed December 1, 2009. Rather, one of ordinary skill in the art would have understood that the method of Ralph is limited to detecting cancers which have reached this metastatic potential or which are metastatic, and could only be extrapolated to performing the methods of detection on other, similar cancers, *i.e.*, those cancers that are metastatic or have metastatic potential. See paragraphs 9 and 11 of Second Declaration of Dr. Mackay filed December 1, 2009. Thus, the teachings of Ralph may only be extrapolated

to identifying early metastatic changes, and are entirely compatible with extension of the method to earlier stages of disease in which metastatic potential has been reached.

For the reasons discussed above, there is no explicit teaching or suggestion that the method of Ralph could be extended or extrapolated to very early stages of cancer such as very early stage breast cancer, in which neither metastasis nor metastatic potential is reached. Also, the Examiner has admitted that Ralph does not teach or exemplify a method in which the organ defined cancer is very early stage breast cancer. See page 6, lines 9-12 of Office Action mailed February 8, 2008 and sentence bridging pages 3-4 of Office Action mailed January 12, 2010. The Examiner's reliance on Lukas for providing the necessary expectation of success because Lukas examines differential gene expression in DCIS samples is flawed. Lukas is entirely silent on whether expression in peripheral blood cells would be affected in stage 0 breast cancer. Rather, the differential gene expression in Lukas is associated with the tumor cells themselves.

In this respect, the Examiner has failed to establish a *prima facie* case of obviousness as "[e]vidence showing there is no reasonable expectation of success may support a conclusion of nonobviousness." M.P.E.P. 2143.02.

Nevertheless, even if, *arguendo*, one of ordinary skill in the art were to attempt to use the method of Ralph for detection of very early stage breast cancer, as explained in paragraph 15 of the Second Declaration by Dr. Mackay filed December 1, 2009, there would have been no reasonable expectation of successfully detecting the altered gene expression of such non-metastatic or pre-metastatic cancers in peripheral blood samples. As discussed above, the method of Ralph relies on the presence of metastatic markers for detection.

3. There would have been no reason or motivation to modify the method of Ralph with the teachings of Lukas to detect very early stage breast cancer, and even if such a modification was made, the claimed invention would not result.

Furthermore, because the teachings of Ralph rely on detection of cancers that have reached metastatic potential or are metastatic, one of ordinary skill in the art would not have been motivated to try the method disclosed by Ralph to detect cancers that have not reached metastatic potential or are non-metastatic.

As detailed above, the cancer cells of Ralph would reflect an altered phenotype and would have begun to release cells, debris or cellular components into the blood system allowing for the interaction of blood cells with the cells, debris or cellular components. In contrast, very early stage breast cancer which is non-metastatic or pre-metastatic does not release such cells, debris or cellular components into the blood system. See paragraphs 7-8 of First Declaration by Dr. Mackay filed March 27, 2009 and paragraph 15 of Second Declaration by Dr. Mackay filed December 1, 2009. Further, there is no teaching or suggestion by Ralph to obtain probes from non-metastatic or pre-metastatic breast cancer patients, or to prepare a gene transcript pattern for the diagnosis of cancers using such probes, as claimed. Rather, Ralph teaches generating probes from blood samples of patients with metastatic breast or metastatic prostate cancer (see paragraph 15 Dr. Mackay's second Declaration filed December 1, 2009).

In this respect, the Examiner has failed to establish a *prima facie* case of obviousness, by failing to "find some motivation or suggestion to make the claimed invention *in light of the prior art teachings* [emphasis added]." M.P.E.P. § 2144.08. In the present case, because Ralph teaches generating probes from blood samples of patients with metastatic breast or metastatic prostate cancer, the teachings of Ralph would have guided one of ordinary skill in the art *away* from the claimed invention. Also, because Lukas is merely cited for teaching markers for very

early stage breast cancer, there would have been no reason or motivation to combine Ralph with Lukas in order to obtain the claimed invention. Pursuant to M.P.E.P. §2141.02, "[a] prior art reference must be considered in its entirely, i.e., ***as a whole including portions*** that would lead away from the claimed invention [emphasis added]." *W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540* (Fed. Cir. 1983); *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997) (holding that a *prima facie* case of obviousness may be rebutted by showing that in the art, in any material respect, teaches away from the claimed invention.).

B. The rejection of claims 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35 as allegedly being unpatentable over Ralph and Lukas as applied to claims 18 and 20-35, and further in view of Wadhwa under 35 U.S.C. § 103(a) should be reversed because a *prima facie* case of obviousness has not been established.

In view of the deficiencies recognized above for Ralph and Lukas, neither Ralph nor Lukas, separately or in combination, teach or suggest all the claimed limitations. M.P.E.P. § 2143. Further, the Examiner has admitted that the combination of Ralph and Lukas fail to disclose a method in which identified isolated nucleic acid markers are prepared on a solid support. See page 6, lines 9-12 of Office Action mailed February 8, 2008.

Wadhwa does not cure the deficiencies of Ralph and Lukas discussed above, and does nothing further to render the claimed invention obvious, because Wadhwa is merely relied upon for teaching a technical assay, *i.e.*, reverse Northern assay of DNA fragments isolated from differential display.

Thus, because neither Ralph, Lukas, nor Wadhwa, separately or combined, teach or suggest that very early stage breast cancer may be detected or diagnosed using non-metastatic or pre-metastatic cancer cells, there would have been no reason or motivation for one of ordinary skill in the art to try to extend the teachings of Ralph to detect non-metastatic or pre-metastatic

cancers because the teachings of Ralph may only be extrapolated to identifying early metastatic changes. Accordingly, one of ordinary skill in the art would not have had a reasonable expectation that the combination would successfully detect and diagnose very early stage breast cancer, as unexpectedly and surprisingly provided by the claimed invention, even in light of Lukas and/or Wadhwa. Further, even assuming arguendo these references are combined, one of ordinary skill in the art would not arrive at the claimed invention for the reasons discussed above and on record.

C. The claimed invention allows for the unexpected detection of non-metastatic or pre-metastatic very early stage breast cancer.

Furthermore, any alleged *prima facie* case of obviousness is overcome because the present invention allows for the unexpected and surprising detection of non-metastatic or pre-metastatic very early stage breast cancer in peripheral blood samples.

As illustrated in the Declaration submitted by the inventor Dr. Praveen Sharma filed September 21, 2007, the claimed method discriminates between normal and very early stage breast cancer (stage 0) patients with high accuracy. The results in the Declaration show a sensitivity of around 80% and a specificity of around 75% for analysis.

In contrast, the experiments of Ralph show only detection of metastatic cancers or those with metastatic potential. As discussed above, because the method of Ralph relies on detection of cancers which have reached a metastatic phenotype and hence have detectable markers of that metastatic phenotype released in peripheral blood cells, analysis of peripheral blood cells to detect non-metastatic or pre-metastatic very early stage breast cancer in which no such phenotypic changes have taken place would have been entirely unexpected.

Indeed, contrary to the Examiner's comments, it is quite remarkable that the claimed method does in fact work. Prior to the present invention, a blood screen capable of diagnosing stage 0 breast cancer was not available. This was not surprising since those cancers are not metastatic, have not reached metastatic potential and have not released cells (or their components or debris) from the breast ducts. Thus the phenotype of the cells has not changed in a detectable way and the cells (or their components or debris) have not been released into the blood. However, despite expectation, the disease state does influence peripheral blood cells sufficient to allow the alteration of gene expression within blood cells. This method offers considerable advantages over the invasive, time-consuming and painful methods of breast cancer diagnosis that were available prior to the present invention. The inventors have therefore made a significant advance over the prior art by providing a simple blood test for diagnosing stage 0 breast cancer.

Thus, the present invention allows the detection of cancers not by extrapolation of Ralph which is concerned with identifying early metastatic changes, but by detection of the pre-metastatic state of the tumor. This was not foreshadowed by Ralph and thus offers a considerable contribution to the art in which early detection is vitally important to improving survival statistics.

The unexpected detection of non-metastatic or pre-metastatic very early stage breast cancer in peripheral blood samples is evidence of the non-obviousness of the claimed methods.

VIII. CONCLUSION

For all the reasons set forth above, Appellant respectfully requests the Board of Appeals to not sustain the rejection of claims 18-35.

The statutory fee (37 C.F.R. §41.37(a) and 1.17(c)) is being remitted. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Tu A. Phan/

Tu A. Phan, Ph.D.
Registration No. 59,392

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: March 1, 2011

CLAIMS APPENDIX

CLAIMS 18-35 ON APPEAL:

1-17. (canceled).

18. A method of obtaining isolated selected mRNA species or isolated selected cDNA species useful for diagnosing or identifying breast cancer in a human comprising the steps of:

(a) isolating mRNA from cells from blood of more than one human who are known to have very early stage breast cancer (breast cancer sample), wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;

(b) isolating mRNA from corresponding cells from blood of more than one normal human (normal sample), wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;

(c) separating mRNA species or cDNA species present within each of the resulting isolated mRNA or isolated cDNA of step (a) and step (b), wherein the resulting separated mRNA species are optionally subject to reverse transcription to obtain separated cDNA species;

(d) selecting 10 or more mRNA species or 10 or more cDNA species from the resulting separated mRNA species or resulting separated cDNA species obtained in step (c), respectively, which are present at a different level in the normal sample than in the breast cancer sample by identifying a signal corresponding to each mRNA species or cDNA species, wherein the resulting selected 10 or more mRNA species are optionally subjected to reverse transcription to obtain 10 or more selected cDNA species; and

(e) isolating the resulting 10 or more selected mRNA species or resulting 10 or more selected cDNA species obtained in step (d) to obtain isolated selected mRNA species or isolated

selected cDNA species, wherein the resulting isolated selected mRNA species are optionally subjected to reverse transcription to obtain isolated selected cDNA species.

19. A method of preparing a gene transcript pattern probe kit comprising the steps of:

(a) isolating mRNA from cells from blood of more than one human who are known to have very early stage breast cancer (breast cancer sample), wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;

(b) isolating mRNA from corresponding cells from blood of more than one normal human (normal sample), wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;

(c) separating mRNA species or cDNA species present within each of the resulting isolated mRNA or isolated cDNA of step (a) and step (b), wherein the resulting separated mRNA species are optionally subject to reverse transcription to obtain separated cDNA species;

(d) selecting 10 or more mRNA species or 10 or more cDNA species from the resulting separated mRNA species or resulting separated cDNA species obtained in step (c) respectively, which are present at a different level in the normal sample than in the breast cancer sample by identifying a signal corresponding to each mRNA species or cDNA species, wherein the resulting selected 10 or more mRNA species are optionally subjected to reverse transcription to obtain 10 or more selected cDNA species;

(e) isolating the resulting 10 or more selected mRNA species or resulting 10 or more selected cDNA species obtained in step (d) to obtain isolated selected mRNA species or isolated selected cDNA species, wherein the resulting isolated selected mRNA species are optionally subjected to reverse transcription to obtain isolated selected cDNA species; and

(f) preparing at least one solid support carrying the resulting isolated selected mRNA species or isolated selected cDNA species of step (e) so as to form a gene transcript pattern probe kit.

20. The method as claimed in claim 18 or 19, wherein said separation in step (c) is performed by a non-sequence based separation technique.

21. The method as claimed in claim 18 or 19, wherein in steps (a) and (b), the resulting isolated mRNA is subjected to reverse transcription to obtain isolated cDNA.

22. The method as claimed in claim 21, wherein said isolated cDNA is amplified.

23. The method as claimed in claim 18 or 19, wherein in step (e), between 50 and 100 mRNA species or cDNA species are isolated and selected.

24. The method as claimed in claim 18 or 19, wherein, in step (e) between 10 and 500 mRNA species or cDNA species are isolated and selected.

25. The method as claimed in claim 18 or 19, wherein, in step (c), said separation technique is gel electrophoresis.

26. The method as claimed in claim 19, wherein, prior to immobilizing in step (f), the resulting isolated selected mRNA species or isolated selected cDNA species of step (e) are amplified.

27. A method of preparing a standard gene transcript pattern characteristic of breast cancer of a human comprising the steps of:

(a) isolating mRNA from cells from blood of more than one human who are known to have said breast cancer (breast cancer sample), wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;

(b) isolating 10 or more mRNA or cDNA species which are present at a different level in cells in a blood sample from more than one normal human than in corresponding cells in a blood sample from more than one human who are known to have very early stage breast cancer according to the method of claim 18;

(c) hybridizing the resulting isolated mRNA or isolated cDNA of step (a) to said 10 or more mRNA or cDNA species of step (b), wherein said mRNA or cDNA species of step (b) are carried on a solid support; and

(d) assessing the amount of hybridization so as to obtain said standard gene transcript pattern.

28. A method of preparing a test gene transcript pattern for breast cancer in a human comprising the steps of:

(a) isolating mRNA from cells from blood of a test human suspected to have breast cancer, wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;

(b) isolating 10 or more mRNA or cDNA species which are present at a different level in cells in a blood sample from more than one normal human than in corresponding cells in a blood sample from more than one human who are known to have very early stage breast cancer according to the method of claim 18;

(c) hybridizing the resulting isolated mRNA or isolated cDNA of step (a) to said 10 or more mRNA or cDNA species of step (b), wherein said mRNA or cDNA species of step (b) are carried on a solid support; and

(d) assessing the amount of hybridization so as to obtain said test gene transcript pattern.

29. A method of diagnosing or identifying breast cancer in a test human comprising the steps of:

(a) isolating mRNA from cells from blood of a test human, wherein the resulting isolated mRNA is optionally subjected to reverse transcription to obtain isolated cDNA;

(b) isolating 10 or more mRNA or cDNA species according to the method of claim 18;

(c) hybridizing the resulting isolated mRNA or isolated cDNA of step (a) to 10 or more mRNA or cDNA species of step (b), wherein said mRNA or cDNA species of step (b) are carried on a solid support;

(d) hybridizing isolated mRNA or isolated cDNA prepared from corresponding cells from blood of more than one human who are known to have said breast cancer to the 10 or more mRNA or cDNA species of step (b) wherein said mRNA species or cDNA species of step (b) are carried on a solid support;

(e) assessing the amount of hybridization in steps (c) and (d) so as to obtain a test and standard hybridization pattern; and

(f) comparing the resulting hybridization patterns obtained in step (e), so as to determine the degree of correlation indicative of the presence of said breast cancer, and so as to diagnose or identify said breast cancer in said test human

wherein the mRNA or cDNA species identified in step (b) are present at a different level in cells in a blood sample from more than one normal human than in corresponding cells in a blood sample from more than one human who are known to have very early stage breast cancer.

30. The method as claimed in claim 27, 28 or 29, wherein in step (a), the resulting isolated mRNA is subjected to reverse transcription to obtain isolated cDNA.

31. The method as claimed in claim 30, wherein said isolated cDNA is amplified.

32. The method as claimed in claim 18, 19, 27, 28 or 29, wherein when isolated cDNA is obtained, any of said isolated cDNA is labeled.

33. The method as claimed in claim 27, 28 or 29, wherein, in step (c), between 50 and 100 mRNA species or cDNA species are used.

34. The method as claimed in claim 27, 28 or 29, wherein, in step (c), between 10 and 500 mRNA species or cDNA species are used.

35. The method as claimed in claim 19, 27, 28 or 29, wherein said solid support is a filter.

36-38. (canceled).

EVIDENCE APPENDIX

Pursuant to 37 C.F.R. § 41.37(c)(1)(ix), submitted herewith are copies of any evidence pursuant to 37 C.F.R. §§ 1.130, 1.131, or 1.132 or any other evidence entered by the Examiner and relied upon by Appellant in the appeal.

Declaration under 37 C.F.R. § 1.132 by Dr. Praveen Sharma filed September 21, 2007, and entered by Examiner as indicated on page 2 of Office Action mailed February 8, 2008.

First Declaration under 37 C.F.R. § 1.132 by Dr. James Mackay filed March 27, 2009, and entered by Examiner as indicated on page 3 of Office Action mailed June 12, 2009.

Second Declaration under 37 C.F.R. § 1.132 by Dr. James Mackay filed December 1, 2009, and entered by Examiner as indicated on page 2 of Office Action mailed January 12, 2010.

RELATED PROCEEDINGS APPENDIX

Submitted herewith are copies of decisions rendered by a court of the Board in any proceeding identified in Section II pursuant to 37 C.F.R. § 41.37(c)(1)(ii).

None.